Chapter 02

Cell Injury and Adaptation

Normal Cell

Under normal conditions cells are in a homeostatic or steady state (homeostasis is a tendency to remain stable). The cell that has the tendency to stable its normal or homeostatic state and is able to handle physiologic demands, is called normal cell.

CELL RESPONSE TO ADVERSE INFLUENCE

Cells react to the unfavorable conditions in the following ways:

- Cellular adaptation
- Cell injury

Cellular adaptation

Adaptation is an adjustment of the cell within limits to the environment in which altered steady state is achieved to preserve the viability of the cell despite continued stress (stress may be physiological or pathological). Examples are discussed below:

Hypertrophy

An increase in the size of an organ or tissue due to increase in the size of the cells e.g. increase in skeletal muscles mass associated with exercise and the enlargement of left ventricle in hypertensive heart disease. Number of cells remains the same.

Atrophy

A decrease in the size of an organ or tissue resulting from a decrease in mass of preexisting cells e.g. tissue atrophy in the period of prolonged starvation or ischemia. Number of cells remains unchanged.

Hyperplasia

An increase in the size of any organ or tissue due to increase in number of cells e.g. uterine enlargement during pregnancy.

Cell injury

When the limits of adaptive capacity are exceeded or when no adaptive response is possible, a consequence of events follows, termed as cell injury. The cell injury may be reversible or irreversible.

- **Reversible cell injury:** It denotes pathologic changes that can be reversed when the stimulus (or stress) is removed or if the cause of injury is mild.
- **Irreversible cell injury:** It denotes pathologic changes that are permanent and cause cell death.

Causes of cell injury	
Hypoxia	Immunologic reactions
Physical agents	Genetic defects
Chemical agents	Nutritional imbalances
Microbiologic agents	

Hypoxia

It means lack of oxygen, which may be due to:

- Ischemia (loss of blood supply) due to arterial occlusion
- Inadequate oxygenation of blood secondary to pulmonary disease
- Loss of oxygen carrying capacity of blood as in anemia or carbon monoxide poisoning
- Decreased tissue perfusion as occurs is hypotension, shock and cardiac failure

Physical agents

- Trauma, radiation, electric shock
- Extremes of temperatures
- Sudden change in atmospheric pressure

Chemical agents

- Glucose or salt in hypertonic concentration
- Oxygen in high concentration
- Poisons e.g. arsenic, cyanide
- Insecticides, carbon monoxide, alcohol
- Drugs

Microbiologic agents

Bacteria, viruses, fungi, parasites

Immunologic reactions

Anaphylactic reaction, autoimmune diseases

Genetic defects

Congenital malformations, sickle cell anemia

Nutritional Imbalances

Hypovitaminosis, protein calorie malnutrition

MECHANISMS OF CELL INJURY

Certain intracellular systems are particularly vulnerable to cell injury and different pathologic stimuli attack these systems through different mechanisms. These important systems are:

- Maintenance of the integrity of cell membrane
- Aerobic respiration and production of ATP
- Synthesis of enzymes and structural proteins
- Preservation of the integrity of the genetic apparatus

These systems are closely related and thus injury to one system leads to wide ranging secondary effects. There are several pathogenic mechanisms through which cell injury can take place. One or more than one of the following biochemical reactions may be involved.

1. Impaired cell membrane function
2. Decreased ATP (energy) production
3. Genetic alteration
4. Metabolic derangement

Impaired cell membrane function

Following mechanisms can damage the cell membrane:

1. Production of free radicals
2. Loss of calcium homeostasis and increased intracellular calcium
3. Activation of complement system
4. Lysis by enzymes
5. Lysis by viruses, heat, cold and certain chemicals

Production of free radicals

Oxygen derived free radicals are chemical species with a single unpaired electron in an outer orbit. When generated in cells, they rapidly attack and degrade nucleic acids and membrane molecules. In addition, free radicals initiate autocatalytic reactions.

Examples of free radicals are superoxide and hydrogen peroxide.

Generation of free radicals

Free radicals may be generated within cells by:

- Normal metabolism (oxidation-reduction reactions)
- Oxygen toxicity
- Ionizing radiation (X-ray, ultraviolet rays)
- Drug and chemicals
- Cellular aging
- Acute inflammation

Mechanism of cell injury by free radicals

- Lipid peroxidation of membrane resulting in cellular and mitochondrial membrane damage
- DNA damage
- Loss of enzymatic activity by promoting cross-linking of proteins

Free radical degradation

Once free radicals are formed, body has protective mechanism to get rid of them. The defense mechanism comprises:

- Intracellular protective enzymes e.g. glutathione peroxidase, catalase, superoxide dismutase
- Antioxidants e.g. vitamin E and C

Loss of calcium homeostasis and increased intracellular calcium

Ischemia and certain toxins cause influx of calcium across the plasma membrane and release calcium from mitochondria and endoplasmic reticulum. This increased intracellular calcium activates phospholipases that degrade membrane phospholipids thus causing cell membrane damage.

Activation complement system

Activation of complements C5b, C6, C7, C8 and C9 membrane e.g. clostridium per fringes bacteria that damage the cell membrane.

Lysis by viruses, heat, cold, certain chemicals

Effects of cell membrane damage

a. Loss of structural integrity

b. Loss of cellular function

Decreased ATP (energy) production

Hypoxia and hypoglycemia result in deficient ATP production. ATP is required for such important processes as membrane transport, protein synthesis, and phospholipid turnover. The effects of ATP depletion will be discussed later in the section of features of reversible and irreversible injury.

Genetic alteration

DNA in the chromosomes represents the genetic basis of control of cellular functions such as synthesis of structural proteins, growth regulating proteins and enzymes. DNA abnormalities may be inherited from generation to generation or acquired by any of several agents e.g. ionizing radiation, viruses, drugs and chemicals.

Effects

- Failure of synthesis of vital intracellular structural proteins
- Failure of mitosis in actively dividing cells e.g. in bone marrow leads to anemia
- Failure of growth-regulating proteins leads to cancer formation

- Failure of enzyme synthesis affects vital biochemical reactions

Metabolic derangemet

Exposure to many exogenous injurious agents such as alcohol, drugs, heavy metals, infectious agents and accumulation of some endogenous substances can damage the cell. This topic will be discussed separately in next pages.

Mechanisms of cell injury

1. **Impaired cell membrane function by**
   - Production of free radicals
   - Loss of calcium homeostasis
   - Activation of complements
   - Lysis of enzymes
   - Direct membrane lysis by viruses, heat, cold and chemicals
2. **Decreased ATP production due to**
   - Hypoxia
   - Hypoglycemia
3. **Genetic alterations**
4. **Metabolic derangement**
   - Exposure to exogenous injurious agents
   - Accumulation of some endogenous substances

ISCHEMIC AND HYPOXIC INJURY

Causes of hypoxic injury

1. Ischemia—lack of blood supply due to obstruction of arterial blood flow
2. Decreased oxygen carrying capacity of blood as in anemia and carbon monoxide poisoning
3. Decreased oxygenation of blood due to respiratory diseases
4. Decreased tissue perfusion as in hypotension and shock

Features of reversible injury

Hypoxia affects mitochondria that results in decreased synthesis of ATP. As a consequence of reduced ATP availability, following changes develop in cellular structure which are reversible if oxygen supply is restored.

1. Cellular swelling
2. Desegregation of ribosomes and failure of protein synthesis
3. Reduced intracellular pH resulting in clumping of nuclear chromatin
4. Appearance of myelin figures and cell blebs due to membrane damage

Cellular swelling

Cellular swelling or cloudy swelling or hydropic change is characterized by the presence of large vacuoles in the cytoplasm. Cellular swelling is the result of failure of cell membrane pump which maintains Na, K balance across the cell membrane. Failure of this Na^+, K^+ ATPase pump due to deficiency of ATP results in accumulation of Na^+ inside and K^+ outside the cell. Excess Na^+ inside the cell exerts osmotic pressure and pulls water inside, resulting in cellular swelling.

It is the first manifestation of all forms of injury to cell in which cell becomes incapable of maintaining ionic and fluid homeostasis resulting in cellular swelling, pale colour, and increased weight of the organ.

The cytoplasm shows:

- Swelling endoplasmic reticulum
- Swelling mitochondria
- Swelling of the whole cell

Desegregation of ribosomes and failure of protein synthesis

Ribosomes become detached from the rough endoplasmic reticulum due to its swelling and therefore protein synthesis is reduced.

Reduced intracellular pH

Decreased ATP synthesis stimulates the enzyme phosphofructokinase activity resulting in increased rate of anaerobic glycolysis that leads to production of pyruvic acid and subsequently lactic acid. Accumulation of lactic acid decreases intracellular pH which causes clumping of cytoplasmic organelles. Disruption of lysosomal membrane leads to release of lysosomal enzymes into the cytoplasm which damage vital intracellular molecules.

Appearance of myelin figures and cell blebs

- Myelin figures: Intracellular whorl-like structures originating from damaged membrane
- Cell Blebs: A cell membrane deformity most likely caused by disorderly function of the cellular cytoskeleton

Features of irreversible injury

Nuclear changes

Nucleus may show one of the three patterns of changes.

- **Karyorrhexis:** The pyknotic nucleus may break into numerous small particles. This process is called karyorrhexis.
- **Karyolysis:** When the nucleus undergoes lysis without pyknosis, the process is called karyolysis.

Cytoplasmic changes

- Irreversible damage to mitochondria manifested by severe vacuolization
- Extensive damage to the plasma membrane
- Massive calcium influx acting as a poison for mitochondria
- Loss of enzymes and proteins due to increased membrane permeability
- Lysosomal swelling and leakage of enzymes
- Injury to the lysosomal membranes results in leakage of their enzymes into the cytoplasm resulting in enzymatic digestion of cell components (autolysis). Leakage of these enzymes into circulation after cell death provides an important means of detecting tissue-specific cellular injury and death in blood serum samples. For example, cardiac muscles contain specific enzyme creatinine kinase. In myocardial infarction, serum level of this enzyme is raised, providing a good indicator of myocardial infarction.

CHEMICAL INJURY

Chemical induced cell injury occurs by one of the two general mechanisms.

- Some chemicals act directly by combining with a critical molecular component or cellular organelle.
- Mostly, chemicals cause injury by aiding in the formation of free radicals.

METABOLIC DERANGEMENT

This is one of the four mechanisms of cell injury and was briefly described earlier. Metabolic derangement may be due to exposure to some exogenous toxic agents or accumulation of some endogenous substances.

Exogenous toxic agents

Some exogenous substances cause cellular damage by interfering directly with various specific biochemical reactions. These substances include alcohol, drugs, heavy metals and infectious agents.

Accumulation of endogenous substances

Proteins, carbohydrate and lipids can accumulate in cells and sometimes cause cellular injury. The processes that result in abnormal intracellular accumulation include:

- **Abnormal metabolism:** In this condition, a normal endogenous substance is produced at a normal or increased rate, but the rate of metabolism is inadequate to remove it. Example: Fatty change in the liver
- **Lack of enzyme:** In this situation, a normal or abnormal endogenous substance accumulates because it cannot be metabolized due to the genetic lack of an enzyme that is necessary for metabolism. Example: Storage diseases e.g. glycogen storage disease

Substances accumulating in tissues as a result of deranged metabolism

Substance	Effects
Water	Edema
Triglycerides	Fatty change
Cholesterol	Atherosclerosis
Protein	Amyloidosis
Glycogen	Glycogen storage disease
Mucopolysaccharide	Mucopolysaccharidosis
Iron	Hemochromatosis
Calcium	Calcification
Copper	Wilson's disease
Bilirubin	Kernicterus, jaundice
Uric Acid	Gout

FATTY CHANGE (STEATOSIS)

Fatty change refers to any abnormal accumulation of triglycerides within parenchymal cells leading to an absolute increase in intracellular lipids. It is an example of accumulation of endogenous substances due to abnormal metabolism.

Common sites

1. Liver: The most commonly affected organ because it is the major organ involved in fat metabolism
2. Heart
3. Skeletal muscles
4. Kidney
5. Any other organ

Causes of fatty liver

- Alcohol abuse
- Diabetes mellitus
- Obesity
- Protein malnutrition (starvation)
- Hepatotoxins
- Drugs
- Pregnancy

Mechanism of fatty liver

Accumulation of triglycerides in the cytoplasm of liver cells occurs due to:

- Increased mobilization of adipose tissue, resulting in an excessive fatty acid entry into the liver cells e.g. in starvation and diabetes
- Rate of conversion of fatty acids to triglycerides in the liver cell is increased due to over-activity of the involved enzyme e.g. due to alcohol
- Decreased oxidation of triglycerides e.g. in anemia and hypoxia
- Decreased synthesis of lipid acceptor proteins such as apoprotein due to protein malnutrition and carbon tetrachloride poisoning

Morphology of fatty liver

Gross

Liver becomes enlarged, yellow, soft and greasy.

Light microscopic

Fatty change is seen as small fat vacuoles in the cytoplasm around the nucleus. As the process

progresses, the vacuoles fuse to form larger globules which displace the nucleus to the cell periphery.

Significance of fatty change

Mild: No effect on cellular function

Moderate: May impair cellular function

Severe: Cellular damage

Note: In most of the conditions, fatty change is reversible if the cause is corrected.

PIGMENTATION

Deposition of coloring material in different parts of the body is called pigmentation.

Exogenous pigments

- **Inhalation:** Carbon, silica
- **Ingestion:** Beta carotene, silver, lead
- **Injection:** Tattooing

Endogenous pigments

- Melanin
- Hemoglobin
- Iron-free pigment e.g. bilirubin
- Iron-containing pigment e.g. hemosiderin
- Lipofuscin

Exogenous pigmentation

In this type, the pigment is introduced in the body from outside by inhalation, ingestion or injection.

Inhalation

Coal dust (carbon) and stone dust (silica) are the commonest substances inhaled. Coal dust produces leaching of pulmonary parenchyma called *anthracosis*. Heavy accumulation of carbon of silica may lead to serious lung damage and fibrosis--the condition called *pneumoconiosis*.

Ingestion

Excessive intake of carrots can lead to yellowish red skin pigmentation caused by carotene. In chronic ingestion of lead, skin has a metallic hue and al blue line appears on the gums.

Injection

Tattooing is the most striking example of pigmentation following injection.

Endogeous pigmentation

These pigments are produced metabolically by tissues of the body itself which get accumulated in the body. Melanin and hemoglobin are two important endogenous pigments.

Melanin

Melanin is an endogenous, brown-black pigment formed in melanocytes when the enzyme tyrosinase catalyzes the oxidation of tyrosine to dihydroxyphenylalanine. It is synthesized exclusively by melanocytes-specific cells characteristically found in the epidermis. Melanin acts as screen and protects the body against harmful ultraviolet radiation of sunlight. Melanin production is stimulated by melanocyte stimulating hormone (MSH) which are released from pituitary gland.

- The cortisol hormone released from adrenal gland has inhibitory influence on melanocyte stimulating hormone.
- Testosterone is important for normal pigmentation in males while estrogen increases pigmentation when given systemically such as in women taking oral contraceptive.

Hyperpigmentation

Generalized hyperpigmentation

- *Addison's disease:* This condition develops due to destruction of adrenal glands thus removing the inhibitory adrenal control

(because cortisol inhibits ACTH and MSH). Secretion of ACTH and MSH proceeds unopposed. Pigmentation is seen on exposed skin surface and mouth.

- *Pregnancy:* In pregnancy, there is increased pigmentation of nipples and genitalia and blotchy appearance on face due to increased estrogen secretion.
- Arsenic poisoning
- Hemochromatosis
- Prolonged treatment with chlorpromazine

Focal hyperpigmentation

- *Freckles:* These areas of depigmentation are present at birth due to some inherited autosomal dominant trait.
- *Cafe-au-lait spots:* These are large pigmented patches in a normal person.
- *Peutz-Jeghers syndrome (familial gastrointestinal polyposis):* This is an inherited autosomal disease comprising multiple polyps of stomach and intestine and a brownish pigmentation around mouth and lips.
- *Lentigo Senilis:* These are multiple smooth liver spots on dorsal surface of hands, face, neck, and arms in old age.

Hypopigmentation

Generalized hypopigmentation

Albinism

This condition is present at birth. The skin is milky white, hair white and iris blue-gray. The number of melanocytes is normal but the melanin pigment is absent. This melanin deficiency is due to congenital lack of tyrosinase enzyme which is required for the synthesis of melanin.

Focal hypopigmentation

- *Leucoderma:* These are white patchy areas of depigmentation present at birth due to some inherited autosomal dominant trait.
- *Vitiligo:* This condition is characterized by sharply defined areas of depigmentation of the skin, commonly of the hands, face and genital area. In the affected areas, melanocytes and melanin are absent. The exact cause is unknown, autoimmune basis is suspected.

Hemoglobin derived pigments

Following are the hemoglobin derived pigments:

- Iron containing pigments—hemosiderin
- Iron free pigments—bilirubin

Hemosiderin

Hemosiderin is a golden yellow to brown, granular, iron containing pigment formed when hemoglobin breaks down in tissues. An increase in total amount of iron in the body is called hemosiderosis. The excess iron accumulates in macrophages and parenchymal cells as ferritin and hemosiderin and may cause parenchymal cell necrosis.

Local hemosiderosis

Local hemosiderosis is common in any tissue that is the site of hemorrhage. Hemoglobin is broken down and its iron is deposited locally, either in macrophages or in the connective tissue, as hemosiderin.

Sites

- Around hematoma, hemorrhagic infarcts
- Pulmonary hemosiderosis due to small hemorrhages which occur in the lung in mitral stenosis and left ventricular failure

Generalized hemosiderosis

If the body is overloaded with iron, hemosiderin is formed in excessive amount which deposits in macrophages throughout the body especially bone marrow, liver and spleen. Overloading of

iron may be due to multiple transfusions (as in thalassemia), excessive dietary iron or excessive absorption of iron in some hemolytic anemias. Generalized hemosiderosis indicates minor iron overload and has no clinical significance. Excessive iron overload that causes organ damage is called hemochromatosis.

Hemochromatosis

Hemochromatosis is characterized by excessive accumulation of body iron, most of which is deposited in heart, liver and pancreas. The difference between hemochromatosis and hemosiderosis is that hemosiderosis does not cause organ damage and shows minor iron overload while in hemochromatosis there is organ damage and it indicates excessive iron overload. Liver fibrosis, heart failure and diabetes mellitus may result from hemochromatosis. Causes of hemochromatosis are the same as described in generalized hemosiderosis such as multiple transfusions, excessive dietary iron intake or excessive absorption of iron in some hemolytic anemias.

Clinical manifestations of hemochromarosis

Pituitary gland	Hypopituitarism, dwarfism, Sexual infantism
Heart	Cardiomyopathy, arrhythmias, Heart failure
Liver	Cirrhosis
Adrenal gland	Addison's disease
Pancreas	Diabetes mellitus
Testes	Testicular atrophy
Skin	Increased pigmentation due to increased melanin production (Bronze diabetes)

Bilirubin

Bilirubin is an iron free yellow pigment of bile formed from the breakdown of hemoglobin by reticuloendothelial system in spleen, liver and bone marrow. Excessive bilirubin in the circulation causes yellowish pigmentation of skin and conjunctive known as jaundice. Causes of jaundice are discussed in special pathology.

PATHOLOGIC CALCIFICATION

Pathologic calcification is the abnormal deposition of calcium salts, together with smaller amounts of iron, magnesium and other mineral.

Types

Abnormal deposits of calcium salts occur in two circumstances.

- Dystrophic calcification
- Metastatic calcification

Dystrophic calcification

Deposition of calcium salts in dead or dying tissue is called dystrophic calcification. This type of calcification may occur despite normal serum calcium level and in the absence of calcium metabolic derangements.

Common sites

Necrotic tissue that is not absorbed:

- Old gaseous lesion of tuberculosis
- Old infarcts
- Old collection of pus
- Dead parasites e.g. Trichinella spiralis, hydatid cysts, schistosome ova
- Old thrombi
- Fat necrosis
- Hematomas (collection of blood) especially when the hematoma is in close association with bone

Degenerating tissues

- Scars
- Atheroma of blood vessels in advanced atherosclerosis

- Chronic inflammatory lesions e.g. chronic abscess, constrictive pericarditis, damaged heart valves
- Tissues in old age e.g. calcification of pineal gland after middle age and costal cartilage in elderly
- Monckeberg's sclerosis: Calcification of tunica media of artery converting it into a rigid tube
- Old cysts
- Degenerative tumors e.g. breast cancer, uterine fibroid, papillary adenocarcinoma of thyroid, cyst adenoma of ovary
- Chondrocalcinosis: Deposition of calcium phosphate crystals in cartilage e.g. calcification of menisci of the knee joint results in chronic arthritis

Pathogenesis

Dystrophic calcification is not dependent on an increased serum calcium level but it results from a change in the local condition of the tissue.

Metastatic calcification

Metastatic calcification is the deposition of calcium salts in normal tissue due to *hypercalcemia* which results from some derangement in calcium and phosphate metabolism.

Causes of hypercalcemia

1. Increased absorption of calcium from the intestine due to:
   - Hypervitaminosis D
   - Excessive milk intake
   - Idiopathic hypercalcemia of infancy
2. Increased calcium mobilization from bone due to:
   - Primary hyperparathyroidism due to adenoma of parathyroid gland
   - Secondary hyperparathyroidism due to hyperplasia of parathyroid gland which occurs in rickets and osteomalacia
   - Malignancy—most common cause of hypercalcemia
   - Immobilization—in bed ridden patients
   - Hyperthyroidism
3. Increased renal absorption of calcium due to:
   - Thiazide diuretics
   - Familial hypocalciuric hypercalcemia

Common sites

- Kidney: Deposition of calcium in the kidney and may lead to renal failure
- Lungs
- Stomach
- Blood vessels
- Cornea

Difference between dystrophic and metastatic calcification

Occurs in previously damaged tissue	Occurs in previously healthy tissue
Serum calcium level normal	Serum calcium level always high
Calcification not caused by hypercalcemia	Hypercalcemia the cause of calcification

NECROSIS

After death, the cell shows no change initially. Then within a few hours autolysis occurs and the cell shows morphological changes by which cell death can be recognized.

Definitions

1. Necrosis refers to a sequence of morphologic changes that follow cell death in living tissue.
2. The morphologic changes caused by the progressive degradative action of enzymes on dead cells is called necrosis.

3. Necrosis is the sum of intracellular degradative reactions occurring after the death of individual cell within a living organism.

Necrosis = cell death + morphological changes

Mechanism of necrosis

Two processes cause the basic morphologic changes of necrosis.

- Enzymatic degradation of cell
- Denaturation of proteins

Enzymatic degradation of cell

In this process, hydrolytic enzymes are derived from lysosomes of invading inflammatory cells (WBC). The enzymatic degradation by this method is called heterolysis. This mechanism leads to liquefactive pattern of necrosis.

Denaturation of proteins

This mechanism leads to coagulative pattern of necrosis and will be discussed in detail in coagulative necrosis.

Types of necrosis

Basic types

- Coagulative necrosis
- Liquefactive necrosis
- Gangrenous necrosis

In special sites

- Fat necrosis
- Fibrinoid necrosis
- Gangrenous necrosis

Coagulative necrosis

In this type of necrosis, the necrotic cell retains its cellular outline for several days. Coagulative necrosis typically occurs in solid organs, such as kidney, heart and adrenal gland usually as a result of deficient blood supply and anoxia.

Examples

- Myocardial infarction
- Necrosis due to hypoxia in all tissues except in brain

Mechanism

The injury and the subsequent increasing acidosis denatures not only the structural proteins but also the enzymic proteins, thus blocking the cellular proteolysis i.e. enzymes that degrade necrotic issue are also destroyed. Denaturation of protein is the basic mechanism of coagulative necrosis.

Morphology

- Basic structural outline of the coagulated cells is preservation.
- The cell, devoid of its nucleus, appears as a mass of coagulated, pink staining homogenous cytoplasm

Liquefactive necrosis

It is that type of necrosis that occurs due to autolytic and heterolysis actions of enzymes that convert the proteins of cells into liquid. Therefore, it is characterized by softening and liquefaction of tissue.

Examples

- Ischemic necrosis of brain
- Suppurative inflammation (pus formation due to pyogenic bacterial and fungal infection)

Mechanism

Enzymatic degradation of protein is the basic mechanism of liquefactive necrosis.

Morphology

- Complete loss of cellular detail
- Cellular outline also destroyed

Caseous necrosis

This type of necrosis is a combination of coagulative and liquefactive necrosis and is characterized by the presence of soft, dry, cheesy homogenous necrotic material. Like coagulative necrosis, it is not liquefied and like liquefactive necrosis, tissue architecture is completely obliterated.

Example

Principally in the center of tuberculous granuloma

Morphology

Microscopically, the necrotic focus is composed of structureless amorphous granular debris enclosed within a ring of granulomatous inflammation. The tissue architecture is completely obliterated.

Necrosis in special sites

Fat necrosis

Fat necrosis occurs in two forms:

- Traumatic
- Enzymatic

Traumatic fat necrosis

It occurs following severe injury to the tissues with high fat content such as the breast, subcutaneous tissue and abdomen.

Enzymatic fat necrosis

This refers to the necrosis in adipose tissue, induced by the action of pancreatic enzymes which are liberated due to trauma to the pancreas or acute pancreatitis.

Fibrinoid necrosis

Fibrinoid necrosis is a type of connective tissue necrosis especially affecting arterial walls. This type of necrosis is seen particularly in two conditions.

1. Auto immune diseases e.g.
   - Rheumatic fever
   - Polyarteritis nodosa
   - SLE
2. Malignant hypertension

Morphology of fibrinoid necrosis

Fibrinoid necrosis is characterized by loss of normal structure and replacement by a homogeneous bright pink-staining necrotic material that resembles fibrin microscopically. Areas of fibrinoid necrosis contain immunoglobulins, complement, albumin, breakdown products of collagen and fibrin.

Note: The term fibrinoid is different from fibrinous which denotes deposition of fibrin as occurs in inflammation.

Morphologic evidence of necrosis

Early changes

In early necrosis, cell is morphologically normal. There is delay of 1–3 hours before changes are apparent on light microscope.

Nuclear changes

Nuclear change are the best evidence of cell necrosis. The nucleus shows the following changes.

- *Pyknosis:* The chromatin of the dead cell clumps into coarse strands, and the nucleus becomes shrunken, dense, and deeply basophilic mass. This process is called pyknosis.
- *Karyorrhexis*: The pyknotic nucleus may break up into numerous small particles, the process is called karyorrhexis.

- *Karyolysis:* The pyknotic nucleus may undergo lysis by the enzyme DNAse.

Cytoplasmic changes

- *Pyknosis:* The chromatin of the dead cell clumps into coarse strands, and the nucleus becomes shrunken, dense, and deeply basophilic mass. This process is called pyknosis.
- Swelling of the mitochondria and disruption of organelle membranes cause cytoplasmic vacuolation.
- Finally, enzymatic digestion of cell by enzymes released by the cell's own lysosomes causes lysis (autolysis).

Biochemical changes

Accumulation of calcium ions in the necrotic cells occurs which activates enzymes that cause cell lysis.

GANGRENE (GANGRENOUS NECROSIS)

Gangrene is the necrosis of tissue with superadded putrefaction (enzymatic decomposition). In other words, gangrene is a clinical condition in which extensive tissue necrosis is complicated to a variable degree by secondary bacterial infection.

Gangrene = Necrosis + Infection + Putrefaction

Causes of gangrene

1. *Arterial obstruction due to:*
   - Thrombosis of an atherosclerotic artery
   - Embolus
   - Diabetes: Atherosclerosis of arteries, loss of sensation resulting in repeated trauma and increased susceptibility to infection lead to gangrene very commonly in diabetic patient
   - Buerger's disease and Raynaud's disease
2. *Infection*
   - Boils, carbuncles
   - Gas gangrene
   - Gangrene of scrotum
3. *Trauma*
   - Crush injuries
   - Pressure sores
4. *Physical agents*
   - Burns
   - Frostbite
   - Chemicals

Clinical types

1. Wet gangrene
2. Dry gangrene
3. Gas gangrene

Wet (moist) gangrene

Wet gangrene is that type of gangrene in which tissue appears moist. It results from severe bacterial infection superimposed on necrosis.

Pathogenesis

- Venous as well as arterial obstruction is present.
- Tissues are moist due to edema and venous congestion.
- Growth of invading bacteria causes the necrotic area to be swollen and appear reddish black with extensive liquefaction.
- Foul smell is due to destruction of protein by bacteria with formation of foul smelling nitrogenous end products such as indol and skatol.
- Blackening of the tissue is due to formation of black iron sulphide by the reaction between iron released from red cells due to hemolysis and H_2S liberated from bacteria.

- Gangrenous tissue is not clearly demarcated from adjacent healthy tissue.

Common sites

- Intestine: In strangulated hernia, volvulus, and intussusception
- Appendix: In appendicitis
- Limbs: Due to sudden occlusion of arteries as in diabetic patient

Complications

1. Local spread
2. Toxemia
3. High mortality rate

Dry gangrene

This type of gangrene results from gradual obstructions of the blood supply. The effected part becomes dry, wrinkled and discolored.

Pathogenesis

- Dry gangrene is a traditional term used to describe infarction of the limbs, it is not true gangrene because the infection in necrotic tissue is insignificant and putrefaction is absent or minimal but it is still described as gangrene. True gangrene is wet gangrene that shows severe infection and putrefaction of tissue with edema and foul smell. Dry gangrene is basically necrosis followed by mummification.
- The necrotic area becomes black due to breakdown of hemoglobin and formation of iron sulfide.
- A line of demarcation is formed between the gangrenous tissue and the adjacent healthy tissue.

Common sites

Limbs, especially foot

Gas gangrene

In this type of gangrene, bacterial infection causes necrosis and then gangrene with abundant gas formation in the tissue.

Gas gangrene = wet gangrene + gas formation

Predisposing factors

Gas gangrene = wet gangrene + gas formation

Gas gangrene may follow the contamination of a wound with the spores of the pathogenic clostridia (anaerobes). The factor essential for spore germination is a reduced oxygen tension that occurs in deep punctured and lacerated wounds and compound fractures. Soil is particularly dangerous because its salts lead to tissue necrosis. Infections by aerobic organism at the same time serve to produce anaerobic environment that is favorable for anaerobic clostridia.

There are two groups of clostridia–saccharolytic and proteolytic clostridia.

Saccharolytic

- Cl. perfringens
- Cl. septicum

Proteolytic

- Cl. sporogenes
- Cl. istolyticum

Saccharolytic organisms liberate powerful exotoxins that produce tissue necrosis, then proteolytic organisms break down the tissue into putrid products.

Pathogenesis (steps in gas gangrene)

- Deep wound → anaerobic condition → invasion by → spores of clostridia
- Necrosis of muscle fiber due to exotoxins of the sacharolytic clostridia
- Fermentation of muscle carbohydrate (glycogen) with formation of lactic acid and gas

- Due to pressure of gas, arterial supply of the area also cut down
- After necrosis, the proteolytic clostridia decompose the dead muscles which become greenish-black in color due to iron sulfide and foul smelling due to nitrogenous end products
- Severe toxemia due to circulating exotoxins manifested by shock

Common sites

1. Muscles
2. Liver

Complications

1. Rapidly spreading gangrene
2. Shock and hemolytic anemia

Treatment of gangrene

- Treatment of predisposing factors
- Amputation: Surgical removal of the gangrene tissue to prevent spreading of infection to the adjacent healthy tissue

Summary of gangrene (gangrenous necrosis)

Dry gangrene

1. Found on exposed parts i.e. extremities
2. Line of demarcation between living and dead cells
3. Arterial blood supply gradually blocked while venous drainage not affected
4. No smell, no gas bubbles, tissue black
5. Minimal infection and putrefaction

Wet gangrene

1. Found on internal organs (and extremities also)
2. No line of demarcation
3. Sudden arterial and venous obstruction
4. Foul smell, edema and black coloration
5. Severe infection and putrefaction

Gas gangrene

1. Found on exposed parts
2. Part swollen due to edema
3. Crepitus (crackling sensation on palpation over the site due to presence of gas)
4. No line of demarcation
5. Caused by contamination of deep wound with spores of clostridia

Gas gangrene = wet gangrene + gas formation

Diabetic foot

Gangrene of foot in diabetic patients is common. It is the wet type of gangrene in which necrosis is superadded by infection and putrefaction.

Predisposing factors

1. *Sensory neuropathy:* Loss of sensation in feet leads to repeated trauma and negligence from patient because there is no pain sensation. The wound becomes infected.
2. *Ischemia:* Atherosclerosis of artery leads to ischemia (decreased blood supply) resulting in tissue damage.
3. *Lower resistance to infection:* Excess sugar in tissues lowers the resistance to bacterial and fungal infection. Infection involves fascia, tendon and bone.

Management

1. Control diabetes.
2. Keep the tissue dry and clean.
3. Give antibiotics.
4. Surgicaly drain pus and debride necrotic tissue.

Apoptosis (necrobiosis)

This term has been used for a mechanism of cell death affecting single cells scattered in a population of healthy cells. It differs from

necrosis population of healthy cells. It differs from necrosis and represents a physiological process by which abnormal and unsuitable cells die and are eliminated.

Significance

This process is important physiologically in balancing cell proliferation and elimination. It is associated with:

- Maintenance of the organ size in adult
- Organ development and remodeling in the embryo
- Physiological atrophy e.g. breasts after weaning

This process is also important pathologically because it is associated with organ atrophy.

CELLULAR ADAPTATIONS

Adaptation is an adjustment of the cell within limits in which the cells modulate their environment to escape injury. We can say that cellular adaptation is a state that lies between the normal and injured cells.

Following are the important adaptive changes:

- *Atrophy:* Decrease in cell size
- *Hypertrophy:* Increase in cell size
- *Hyperplasia:* Increase in cell number
- *Metaplasia:* Change in cell type

Atrophy

Shrinkage in the size of the cell by loss of cell substance is known as atrophy. Atrophic cells may have diminished function.

Causes

1. **Ischemia:** Diminished blood supply leads to reduction in oxygen supply and nutrients to the tissue or organ resulting in ischemic atrophy.

   Example: Narrowing of coronary arteries results in ischemic atrophy of myocardium.
2. **Reduced functional activity:** Immobilization or inactivity of a tissue or organ leads to atrophy because tissue demand for nutrition is reduced. This type of atrophy is called disuse atrophy.
3. **Interrupted nerve supply:** Skeletal muscle is dependent on its nerve supply for normal function and structure. Damage to the nerve supply leads to rapid atrophy of the muscle fibers supplied by that nerve. This type of atrophy is also called denervation atrophy.

   Examples: Atrophy of skeletal muscles after destruction of nerves in poliomyelitis.
4. **Endocrine deficiency:** Hormonal deficiency causes reduced metabolic activity in dependent tissue resulting in atrophy e.g. deficiency of pituitary hormones leads to atrophy of thyroid, adrenal glands, gonads and genital organs.
5. **Pressure:** Atrophy is produced by a persistent pressure on a tissue or organ which may either causes injury to the cell or interfere with its blood supply or lymphatic drainage e.g. tumor pressuring on surrounding tissues.
6. **Lack of nutrients:** Atrophy is produced by lack of nutrients such as in protein-caloric malnutrition.
7. **Senile atrophy:** This occurs in old age.

Types of atrophy

1. Ischemic atrophy
2. Disuse atrophy
3. Denervation atrophy
4. Pressure atrophy
5. Atrophy due to endocrine deficiency
6. Atrophy due to lack of nutrients
7. Senile atrophy

Hypertrophy

It refers to an increase in the size of cells resulting in enlargement of a tissue or organ without any change in the number of cells.

Types

1. **Physiological:** E.g. the growth of the uterus during pregnancy stimulated by estrogen hormone
2. **Adaptive:** E.g. enlargement of cardiac and skeletal muscle due to overwork. They enlarge because they are unable to produce more cells by mitotic division to share the work.
   - Left ventricular hypertrophy in hypertension
   - Right ventricular hypertrophy in pulmonary hypertension

Hyperplasia

Hyperplasia is the increase in the number of cells resulting in an increased volume of the organ or tissue.

Hyperplasia can only occur in the cells capable of mitotic division in postembryonic life, when stressed or stimulated to increase activity.

Types

Physiological hyperplasia

Hormonal

- Glandular proliferation of the female breast occurs at puberty and during pregnancy and lactation.
- Uterus during pregnancy shows hyperplasia in response to increased level of ovarian steroids.

Compensatory

Hyperplasia in the remaining kidney when the other is removed or destroyed, therefore workload on the remaining kidney is increased.

Pathological hyperplasia

It occurs usually due to excessive hormonal stimulation of target cell e.g.

- Adenomatous hyperplasia of endometrium due to excessive estrogen stimulation
- Thyroid hyperplasia—in primary hyperthyroidism
- Epidermal hyperplasia—in chronic irritation of skin

Clinical significance

Hyperplasia may produce clinical diseases e.g. endometrial bleeding, thyroid hyperfunction etc.

Metaplasia

It is a reversible change in which one adult cell type (epithelial or mesenchymal) is replaced by another adult cell type.

It represents an adaptive substitution of cells more sensitive to stress by other cell types better able to withstand the adverse environment.

Types

Epithelial

- The abnormal pseudostratified columnar ciliated epithelium of the trachea and bronchi is replaced by stratified squamous epithelium in response to chronic irritation, as in chronic cigarette smokers.
- Stones in the excretory ducts of pancreas or bile ducts may replace normal columnar epithelium by stratified squamous epithelium.
- Vitamin A deficiency also produces squamous metaplasia in respiratory epithelium.
- Squamous epithelium of esophagus is replaced by glandular mucus secreting columnar epithelium as a result of acid reflux into the esophagus (causing Barrett's esophagus).

- The glands of endocervix frequently undergo squamous metaplasia in chronic cervicitis.

Clinical effects

- Although the squamous metaplastic cells in respiratory tract are capable of surviving, yet an important protective mechanism of mucous secretion is lost (normal epithelium is secretory while metaplastic is nonfunctional).
- There is an increased risk of neoplasm.

Mesenchymal

Metaplasia of fibroblast to osteoblast may follow the scarring. Thus bone is formed in the area of injury.

Clinical effects

- Epithelial metaplasia is almost always reversible, but the mesenchymal (connective tissue) metaplasia is irreversible.
- Epithelial metaplasia is more common than the mesenchymal metaplasia.

MCQs

1. Conditions causing cell injury by means of free radicals are:
   - T a. Ionizing radiation
   - T b. Ischemia and hypoxia
   - T c. Chemical injury
   - T d. Inflammatory damage
   - T e. Oxygen toxicity

2. Following are the features of reversible injury:
   - T a. Swelling of mitochondria and endoplasmic reticulum
   - T b. Detachment of ribosomes from endoplasmic reticulum
   - T c. Clumping of nuclear chromatin
   - T d. Appearance of myelin figures and cell blebs
   - F e. Pyknosis and karyolysis of nucleus

3. Tissues more vulnerable to ischemia are:
   - T a. Brain
   - T b. Cardiac muscles
   - T c. Connective tissue
   - T d. Skeletal muscle
   - T e. Bone

4. Mechanism of free radical injury include:
   - T a. Lipid peroxidation of cell membrane
   - T b. Inactivation of enzymes
   - T c. Lysosomal enzymes leakage
   - T d. DNA damage
   - T e. Cell membrane damage

5. The substances that protect from free radicals (antioxidants) are:
   - T a. Vitamin "E"
   - T b. Catalase
   - T c. Ceruloplasmin
   - T d. Glutathione peroxidase
   - T e. Superoxide dismutase

6. Features of necrotic cell include:
   - T a. Increase eosinophilia
   - T b. Cytoplasmic vacuolation
   - T c. Karyerexis
   - T d. Swelling of mitochondria
   - T e. Disruption of cytoplasmic organelle

7. Causes of fatty liver are:
   - T a. Alcohol abuse
   - T b. Diabetes mellitus
   - T c. Typhoid fever
   - T d. Obesity
   - T e. Starvation

8. Causes of generalized hyperpigmentation are:
   - T a. Addison's disease
   - T b. Peutz-Jeghers syndrome
   - T c. Freckles
   - T d. Pregnancy
   - T e. Vitiligo

9. The most commonly affected organs by hemochromatosis are:
   - T a. Liver (cirrhosis)
   - T b. Pancreas (diabetes)
   - T c. Heart (arrhythmia)
   - T d. Tongue
   - T e. Testes

10. Metastatic calcification occurs in:
    - F a. Old infarcts
    - F b. Hematoma
    - T c. Kidney (renal papilla)
    - T d. Lungs
    - T e. Cornea

11. Fibriniod necrosis is seen in:
    - T a. Rheumatic fever
    - T b. Polyarteritis nodosa
    - T c. SLE
    - T d. Malignant hypertension
    - F e. Essential hypertension

12. Following are the examples of disuse atrophy:
    - F a. Atrophy of myocardium due to narrowing of coronary arteries
    - T b. Atrophy in paralytic limb
    - T c. Atrophy of exocrine gland due to obstruction of gland duct
    - F d. Malignant hypertension
    - F e. Atrophy of tissue due to pressure from expanding tumor

13. Liquefactive necrosis occurs in:
    - T a. Brain
    - T b. Spleen
    - T c. Kidney
    - T d. Heart
    - T e. Suppurative inflammation (pus formation)

14. Metaplasia:
    - F a. Only occurs in epithelium
    - T b. Characterized by replacement of one cell type to another cell type
    - T c. Occurs in urinary bladder due to schistosome infection
    - T d. Occurs in esophagus
    - F e. Is irreversible

15. Fat necrosis is associated with:
    - T a. Pancreatitis
    - T b. Trauma to breast
    - F c. Hyperlipidemia
    - T d. Trauma to subcutaneous tissue
    - F e. Fatty liver

16. Fatty change in liver:
    - T a. Occurs due to chronic excessive intake of fat
    - T b. Results from increased triglycerides synthesis
    - T c. Results from decreased fatty acid oxidation
    - F d. Result from increased lipoprotein synthesis
    - T e. Results from increased fatty acid synthesis